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A Case of Neonatal Early-Onset Sepsis Due to Citrobacter Koseri Chorioamnionitis

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Abbreviations:

EOS: early-onset sepsis, LOS: late-onset-sepsis, CSF: cerebrospinal fluid, PROM: preterm rupture of the membrane, IAP: intrapartum antibiotic prophylaxis, CNS: central nervous system, PPROM: preterm premature rupture of membranes, MAP: mean airway pressure, PEEP: positive end expiratory pressure, PIP: peak inspiratory pressure, NICU: neonatal intensive care unit, CRP: C-reactive protein, HR: heart rate, PPV: positive pressure ventilation, BE: base excess, HFOV: high-frequency oscillatory ventilation, FiO2: fraction of inspired O2, RDS: respiratory distress syndrome, iNO: inhaled nitric oxide, PH: pulmonary hypertension

1. Abstract

Early-onset sepsis (EOS) remains a serious and often fatal disease of the newborn, particularly in preterm and very low-birth-weight infants. Group B Streptococcus and E. coli are the most common aetiological agents, although other gram-negative organism such as Citrobacter koseri (gram-negative bacillus of the Enterobacteriaceae family) can be found in preterm infants. Nosocomial outbreaks of C. koseri are common, but vertical transmission is less common. Preterm premature rupture of membranes (PPROM), caused by C. koseri, has rarely been described. C. koseri has a strong predilection for central nervous system (CNS), and infections without CNS involvement are rarely described. We report a case of early-onset neonatal sepsis caused by Citrobacter koseri chorioamnionitis at the beginning of the third trimester, which resulted in death despite appropriate neonatal antibiotic treatment.

2. Introduction

Neonatal sepsis is a potentially life-threatening systemic bacterial, viral or fungal infection, that occurs in the first 28 days of life. Depending on the time of onset, it is classified as early-onset sepsis (EOS) or late-onset sepsis (LOS) [1,2].

EOS is an infection usually vertically transmitted from mother to newborn, that presents with clinical signs within the first 72 hours of life. EOS in preterm infants is defined as positive blood or cerebrospinal fluid (CSF) culture obtained within 72 hours of birth [3].

In high-income countries, the most common aetiological agents responsible for EOS are Group B Streptococcus (38% to 58% of cases) and Escherichia coli (18% to 29% of cases); together they account for approximately 70% of all cases of EOS. Other common organisms in EOS are Listeria monocytogenes, other streptococci species, enterococci, staphylococci, Bacillus species, and Haemophilus influenzae [4]. In very low birth weight preterm infants, gram-negative organisms are the predominant EOS pathogens (E. coli is responsible for 50% of cases) [2, 5].

The most common risk factors for EOS are preterm premature rupture of the membrane (PPROM), prolonged PROM (>18 hours), maternal intrapartum fever, chorioamnionitis, urinary tract infection, meconium aspiration, and multiple gestation. In addition, prematurity and low birth weight are major risk factors for the de-

velopment of EOS, also because preterm infants are particularly immunocompromised due to a very immature immune system [4, 6].

The incidence of EOS is approximately 0,3 to 1 per 1000 live births in high-income countries and it is estimated to increase up to 11 per 1000 live births with decreasing gestational age and birth weight. EOS is less common than LOS [4].

Despite the introduction of intrapartum antibiotic prophylaxis (IAP) and all the advances in diagnosis and treatment, sepsis remains associated with a significant risk of mortality in the neonatal population, particularly in preterm and low birth weight infants [2].

Citrobacter koseri (formerly known as Citrobacter diversus) is a facultative anaerobic, non-sporeforming, gram-negative bacillus. It belongs to the family Enterobacteriaceae and is commonly found in water, soil, food and as a coloniser of the gastrointestinal tract [7]. Bacteria of the genus Citrobacter can rarely cause sepsis in newborns and in immunocompromised patients [8]. In neonates, C. koseri has a strong predilection for central nervous system (CNS) involvement, causing meningitis, pneumocephalus and brain abscesses, which develop in approximately 76% of C. koseri infections. The mortality rate for meningitis is between 4 and 30%. Approimately 80% of survivors suffer from chronic CNS damage [9-11]. Clinical signs of CNS infection due to C. koseri are similar to those of other pathogens and include vomiting, poor feeding, hypotonia, lethargy and bulging fontanel. Citrobacter koseri is also a rare cause of neonatal sepsis or bacteriemia without CNS disease [8, 12]. Paediatric respiratory disease due to C. koseri is rare; only a few cases of lung abscess due to C. koseri have been described in the literature [13, 14]. A single case of C. koseri urinary tract infection, sepsis, meningitis, and brain abscess in a 10-day-old neonate with antenatally diagnosed hydronephrosis has also been reported [15]. Overall, the strongest affinity of this bacterium is for brain tissue, and CNS involvement is almost always described in neonatal sepsis caused by C. koseri.

C. koseri can be acquired by vertical maternal transmission at delivery or by transplacental transmission, although only a few cases have been described [7]. Much information is still lacking on the vertical transmission of C. koseri. The other mode of transmission is the horizontal nosocomial spread. Several nosocomial outbreaks resulting in colonisation or disease have been described. It seems clear that horizontal transmission of C. koseri is much more common than vertical transmission [8, 16].

Antibiotics remain the mainstay of treatment for neonatal Citrobacter infections, but surgical drainage of brain abscesses is also widely used [8]. Intravenous ampicillin and an aminoglycoside are still recommended for initial empiric treatment of suspected bacterial septicaemia in neonates. If gram-negative meningitis is strongly suspected, the addition of a third-generation cephalosporine is recommended [9]. The recommended treatment for Citrobacter sepsis with or without CNS involvement is the same as the empiric regimen (ampicillin + aminoglycoside). Dran et al. suggest a third-generation cephalosporin and an aminoglycoside as first-line treatment [8]. Some case reports have also reported the use of carbapenems with mixed results (2 eradications of C. koseri after abscess formation, 1 eradication before abscess formation and 1 death) [17-20]. Association of ciprofloxacin and meropenem has also been successfully used [9].

We report a new case of EOS due to transplacental transmission of C. koseri in an extremely low birth weight preterm infant, apparently without CNS involvement and with severe respiratory involvement.

3. Case Report

A 33-year-old woman was admitted to the emergency department of our hospital for PPROM at 24 weeks and 4 days of gestation. The patient was nulliparous with a previous spontaneous abortion. The pregnancy had a physiological course, except for gestational hypothyroidism. On admission, the rectal-vaginal swab and urine culture were negative. These investigations were not repeated in the following days. During the hospitalisation, the patient had fever and elevated inflammatory markers. Ampicillin was initially administered, then changed to amoxicillin-clavulanic acid and clarithromycin. At 26 weeks' gestation, the mother's C-reactive protein was 312 mg/L (normal value <10) and her white blood cell count was 11530/mmc. Fetal movements were reduced, and the cardiotocography showed fetal distress. Urgent caesarean section was performed at 26 weeks and 1 day of gestation. At birth, the neonate was hypotonic, and the respiratory drive was absent, even after tactile stimulation. The heart rate (HR) was approximately 60 bpm. He was treated with positive pressure ventilation (PPV) (PEEP 5 cmH2O, PIP 25-30 cmH2O) for the persistent bradycardia. At 3' of life, the infant was intubated due to persistent bradycardia, and lack of respiratory drive. After endotracheal intubation, there was an immediate increase of HR and a progressive decrease in FiO2 (from 100% to 60-70%). Body temperature remained between 36.5 and 37°C. Apgar score was 4-6-8 and birth weight was 995 g. The pH at birth from funicular blood gas analysis was 7.24, base excess (BE) -6.6 mmol/L, lactate 6.37 mmol/L. In the NICU, the infant was ventilated with high-frequency oscillatory ventilation (HFOV) with increasing mean airway pressure (maximum MAP of 17 mmHg) to attempt a lung recruitment (FiO2 70-100%). Umbilical venous and arterial catheters were placed. Surfactant was tracheally administered (Poractant, Chiesi (R) 200 mg/kg plus 100 mg/kg) because the high FiO2 requirement and the respiratory distress syndrome (RDS) pattern on lung ultrasound and chest X-ray. In view of the persistently low blood pressure and echocardiographic findings of cardiac failure, dopamine and dobutamine i.v. infusions (both 5 γ/kg/min) were administered in addition to repeated normal saline boluses. Trometamol and bicar-

bonate were administered (BE -9.9 → -18.7 mmol/L, $HCO3^{-}$ 17.4 → 9.7 mmol/L). Packed red blood cells were administered due to anaemia (Hb 10.8 g/dl). In view of the decrease in O2 saturation at FiO2 80% and systemic hypotension, mechanical ventilation was changed from HFOV to pressure-assist control ventilation plus volume guarantee (Vt set at 5-6 ml/Kg). Inhaled nitric oxide (iNO) was administered for pulmonary hypertension (PH). Ampicillin and netilmicin were given for EOS; cefotaxime was added because of the high risk of gram-negative aetiology.

At 4 hours of age, a lung ultrasound was performed due to bradycardia and desaturation (despite FiO2 100%), showing a white lung pattern on the right chest and a massive pneumothorax, with mediastinal shift and hypokinetic cardiac function, on the left side. Emergency pneumothorax needle aspiration was performed, followed by chest tube placement. End-procedure ultrasound and radiographs documented partial resolution of the pneumothorax. An increase in dopamine (10 γ/kg/min) was required after the procedure.

Despite all the efforts, the clinical condition remained extremely critical. The patient was pronounced dead 12 hours after admission to the NICU.

Cranial ultrasounds performed during the hospitalisation were always normal for gestational age, with no signs of abscess, oedema or meningitis. Lung ultrasounds and chest x-rays showed significant respiratory distress syndrome (resistant to surfactant administration) and massive pneumothorax (endotracheal tube persistently well placed).

The infant's blood culture and the placental cultures were positive for Citrobacter koseri (sensitive to cefotaxime and gentamicin). Antibiotic treatment was not effective, although the bacterium was sensitive to the antibiotics used, considering the antibiogram. CSF analyses were not performed due to the patient's critical conditions. No autopsy was carried out by parental will.

4. Discussion

We report a case of EOS due to vertically transmitted Citrobacter koseri, with rapid clinical deterioration leading to mechanical ventilation (from the third minute of life) and inotropic support, complicated by the development of pulmonary hypertension and massive pneumothorax, with exitus in approximately 12 hours.

Neonatal infection caused by Citrobacter koseri is rare. Most cases reported in the literature of neonatal disease due to C. koseri describe meningitis and CNS involvement. The frequency of bacteraemia or sepsis without meningitis is uncertain [8]. Occasionally, other focal infections occur in infants, but this appears to be rare and case reports without CNS involvement are very few [13, 21, 22]. Our case report describes a sepsis due to C. koseri without abscesses on cranial ultrasound, which could be explained by the short time of infection before the infant's death and/or the immature fetal/neonatal immune response. We didn't do a CSF culture because of the critical condition of the infant. In our neonate, pulmonary involvement was predominant, with pulmonary hypertension (PH) and pneumothorax.

Little information is available on the risk of vertical transmission of Citrobacter. Vertical transmission from mother to infant may occur at birth or prenatally. Definite acquired prenatal infection has been documented in a few cases where the bacterium was isolated from the placenta or neonate a short time after birth [7, 8, 16, 23]. Whether prevention of vertical transmission is possible or feasible is unknown, as it has rarely been described. The neonatal epidemiology of C. koseri is still poorly understood and in most cases the source of the organism is unknown. Several well-documented nosocomial outbreaks resulting in colonisation or disease have been described [1, 8, 24, 25]. Nursery precautions are mandatory, as preterm infants are at higher risk of C. koseri infection, and infection control procedures must be implemented immediately in the event of a nursery outbreak [7, 26, 27]. Our case report describes vertical transmission of C. koseri (chorioamnionitis in the early third trimester), resulting in a fulminant early-onset neonatal sepsis. No nursery outbreak was observed following this case.

Neonatal sepsis due to C. koseri has been treated with a variety of antibiotics and surgery if cerebral abscesses are present [8]. The recommended treatment for confirmed Citrobacter sepsis/meningitis does not differ from the empirical regimen with i.v. ampicillin and an aminoglycoside as first-line treatment and the addition of a third-generation cephalosporin when CNS involvement is suspected [9]. Treatment should be given for at least 2 weeks for sepsis alone, at least 3 weeks for uncomplicated meningitis, and 4-6 weeks for brain abscesses. Surgical drainage should also be considered for abscesses [8]. Cases of systemic infection or meningitis caused by C. koseri treated with ciprofloxacin and meropenem have also been reported in the literature [9]. An ideal antibiotic for C. koseri infection in neonates must have bactericidal activity and be able to readily cross the blood-brain barrier and enter neutrophils intracellularly to reach C. koseri harboured in CSF macrophages. In addition, the antibiotic must have an acceptable toxicity profile in neonates. Taking these criteria into account, ciprofloxacin and meropenem should be optimal options and have even been proposed as the first-line treatment of C. koseri infections, but further studies are needed [9, 28]. In our case, we added a third-generation cephalosporin to the empirical treatment of septicaemia (ampicillin and aminoglycoside) because of a strong suspicion of gram-negative sepsis, given the prematurity and extremely low birth weight. However, the antibiotic treatment was not effective, probably because the infant was already deeply septic before birth.

5. Conclusion

Despite an increasing number of reports, neonatal infections due to Citrobacter koseri are still rare and poorly understood. These infections have a high mortality rate (up to 30%) and unfortunate-

ly about 80% of surviving neonates have chronic CNS damage. It seems clear that C. koseri has a predilection for the CNS, in contrast to the few cases of sepsis or other site infections without neurological involvement. Our case report describes an infant with EOS due to C. koseri and apparently without CNS involvement. Furthermore, we describe a transplacental transmission, whereas nursery outbreaks (horizontal transmission) are more commonly described in the literature. The first-line treatment of C. koseri sepsis is antibiotic therapy with an aminoglycoside and a third-generation cephalosporin, possibly combined with surgical drainage in the presence of cerebral abscesses. Other antibiotics such as ciprofloxacin and meropenem have also been used. Our treatment was appropriate, also considering the antibiogram, but not effective. It is likely that the newborn was already too sick at birth, and perhaps a different type of antenatal antibiotic treatment would have made a difference. More research and systematic reviews on neonatal C. koseri infections are needed.

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